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| EXAMINER | |
|---|---|
| WHITEMAN, B | |
| ART UNIT | PAPER NUMBER |
| 1633 | 17 |

DATE MAILED: 07/18/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/380,203 | Applicant(s) DE LA MONTE ET AL. | |
|---|---|---|---|
| | Examiner Brian Whiteman | Art Unit 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *7-9 and 14-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 10-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2,9 & 13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Priority*

Priority to PCT/US98/03685 filed on 26 February 1998 is acknowledged.

### *Information Disclosure Statement*

The information disclosure statement filed on February 14, 2000 does not fully comply with the requirements of 37 CFR 1.98 because: applicant does not properly cite the journal article(s) listed on the 1449. The foreign patent document is in German and the examiner does not read or speak German. The foreign patent will be considered to the extent of the English abstract since AS5 is an English abstract of the German patent. In addition, the 1449 filed on January 2, 2001 is missing articles AS5-AT6. Furthermore, IDS filed December 3, 1999 is missing.

The examiner has considered the references (except for AS5-AT6 and AL1 (entire document). If applicant wants these references initialed and dated on the 1449, an English translation of the entire document (AL1) is required and the journal articles (AS5-AT6) must be filed with the response to this office action. Failure to comply with this notice will result in the above mentioned information disclosure statement being placed in the application file with the non-complying information not being considered. See 37 CFR 1.97(i).

Applicants elect invention of Group I, represented by claims 1-6 and 10-13 made without prejudice in paper nos.16, and filed 25 June 2001 is acknowledged.

Claims 7-9 and 14-34 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 16.

Elected claims 1-6 and 10-13, to which the following grounds of rejection are applicable, are pending examination.

Claim 4 is objected to as being dependent upon a rejected base claim (claim 1), but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 1 and 11 are objected because of the following informalities: two periods in a claim. Instead of Seq. ID No. 2, replace with Seq ID NO: 2.

Claim 3 is objected to because of the following informalities: incorrect spelling of virion. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1, as best understood, is readable on a genus of a DNA molecule of Seq ID No: 1 or a DNA molecule which is at least 40% homologous to Seq ID No: 1, or a fragment thereof, wherein the genus of the DNA molecule is not claimed in a specific biochemical or molecule structure that could be envisioned by one skilled in the art at the time the invention was made.

The specification contemplates fragments of the DNA molecule that code for proteins having the activity of Seq ID NO: 1, which induces neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites in a host which expresses the DNA sequence (page 18, lines 28-30 and page 20, lines 1-2). The disclosure provides sufficient description for a cDNA designated AD7c-NTP (Seq ID No: 1) possessing the

biological properties listed above. However, the specification does not provide sufficient description of a genus of polynucleotide sequences that possess any of the biological characteristics of Seq ID No: 1. It is not apparent that on the basis of the applicants' disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the claimed invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of DNA sequences that must exhibit the disclosed biological functions as contemplated by the specification.

It is not sufficient to support the present claimed invention directed to a genus of polynucleotide sequences, which induce neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites in a host. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of a DNA molecule of Seq ID No: 1 and/or a DNA molecule which is at least 40% homologous thereof, that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan

cannot envision the detailed structure of a genus of a DNA molecule, which displays at least 40% homology to Seq ID no: 1 that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-6 and 10-13, as best understood, are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

1) A DNA construct, which encodes the polynucleotide sequence of AD7c-NTP (Seq ID No: 1), wherein, said AD7c-NTP is under control of a heterologous neuro-specific promoter.

2) The DNA construct of claim, which is contained within a vector.

3) The DNA construct of claim 1, which is contained in a virion.

4) An in vitro host cell transformed with the DNA construct of claim 1.

5) The in vitro host cell line of claim 5, which is a neuronal cell.

6) The in vitro method for screening a candidate drug that is potentially useful for the treatment or prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas, and glioblastomas, which comprises

(a) administering a candidate drug to the host cell line of claim 5, and

(b) detecting at least one of the following:

(i) the suppression or prevention of expression of the protein encoded by the said DNA comprising Seq ID No: 1;

(ii) the increased degradation of said protein encoded by said DNA; or

(iii) the reduction of frequency of at least of an one neuritic sprouting, a nerve cell death, a degenerating neurons a neurofibrillary tangles, irregular swollen neurites and axons in the host; due to the drug candidate compared to a control which has not exposed to the candidate drug.

7) The method of claim 7, wherein said protein has Seq ID no: 2.

8) The method of claim 7, wherein said protein is over-expressed by said host cell.

9) The method of claim 7, wherein said cell is a neuronal cell.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Specifically, since the claimed invention is not supported by a sufficient description (for possessing a genus of a DNA molecule encoding at least 40% homology to Seq ID No: 1) as recited in the claims, particularly in view of the reasons set forth above, one skilled in the art would not have known how to make and use the claimed invention so that it would operate as intended, e.g. said DNA molecule that codes for a protein having which induces neuritic

sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites in a host.

In view of the state of the art and the as-filed specification, it is apparent that one skilled in the art would be able to determine a DNA sequence with 40 percent identity to Seq ID No: 1. However, it is not apparent to one skilled in the art if the nucleic acid sequence with at least 40 percent homology to Seq ID No: 1, would exhibit the same biological function of Seq ID No: 1. Since, the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Chiu et al., *Folding and Design*, 1998, pp. 223-228), it would required undue experimentation for one skilled in the art to arrive at other polynucleotides sequences that have Seq ID No: 1 activity. In addition, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for the determination of other genetic sequences that are embraced by the claim. This is the case here. In other words, since it would require undue experimentation to identify other DNA sequences that have Seq ID No: 1 activity, it certainty would require undue experimentation to make their corresponding DNA and, therefore, any other sequences besides the full length cDNA of Seq. ID No: 1 are not enabled.

In addition, claim 5 and claims dependent thereof, as best understood, are readable on an in vitro and in vivo host cell transformed with the DNA construct, which comprises a DNA

molecule of Seq ID No: 1 or a DNA molecule which is at least 40% homologous thereto, or a fragment thereof; wherein said DNA molecule is under control of a heterologous neuro-specific promoter is not enabled. Specifically, since the claimed invention is not supported for using other sequences besides the full length cDNA of Seq ID NO: 1, particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, *e.g.* contacting a candidate drug with said host cell. The as-filed specification provides sufficient guidance for an in vitro host cell transformed with the DNA construct of claim 1, but does not provide sufficient guidance for an in vivo host cell transformed with the DNA construct of claim 1. Furthermore, and with respect to claims directed to any and/or all DNA construct useful for gene therapy and directed to any and/or therapeutic treatments of a mammal; the state of the art in 1998, exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson indicates that the state of the art before 1998, and teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed recombinant retrovirus generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any and/or all nucleic acid therapy methods as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any/or all mammals was unpredictable after the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any and/or all of the gene delivery vectors cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the claimed invention encompassing claims 1-9, listed above. Given the state of art for transforming an in vivo host cell, one would have to engage in a large quantity of experimentation in order to practice the full scope of the claimed invention based on the application's disclosure, the unpredictability of the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) (Chiu et al., *Folding and Design*, 1998, pp. 223-228). In addition, the presence of a working example as provided in the specification does not extrapolate to the full scope of the claimed invention, particularly given that there is no evidence that the DNA sequence (Seq. ID No 1) of AD7c-NTP is a general phenomenon for any sequence with at least 40% homology to Seq. ID No. 1.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 10 recites the limitation "protein coded for by the DNA construct" in lines 5-6, page 63. There is insufficient antecedent basis for this limitation in the claim. It is not apparent

what protein is being used since the base claim (claim1) comprises a DNA molecule of Seq ID No: 1 and/or possibly another protein.

Claims 11-12 recite the limitation "said protein" in lines 15 and 17, page 63. There is insufficient antecedent basis for this limitation in the claim. It is not apparent what protein is being overexpressed since the base claim (claim 1) comprises a DNA molecule of Seq ID No: 1 and/or possibly another protein. In addition, it is not apparent what protein has Seq ID No: 2 in claim 11 for the same reason listed above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. Tracey Johnson whose telephone number is (703) 305-2982.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on M-F, (730-400 EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached at (703) 305-4051.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 746-5024.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-8724.

Brian Whiteman
Patent Examiner, Group 1633
July 13, 2001

DAVE T. NGUYEN
PRIMARY EXAMINER